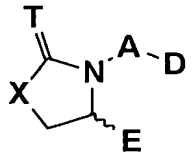
CLAIMS

1. An 8-azaprostaglandin derivative compound represented by formula (I):



(I)

wherein T is (1) an oxygen atom or (2) a sulfur atom;

X is (1) $-CH_2-$, (2) -O- or (3) -S-;

A is A^1 or A^2;

A^1 is (1) C2-8 straight-chain alkylene optionally substituted by 1 to 2 C1-4 alkyl(s), (2) C2-8 straight-chain alkenylene optionally substituted by 1 to 2 C1-4 alkyl(s) or (3) C2-8 straight-chain alkynylene optionally substituted by 1 to 2 C1-4 alkyl(s);

A^2 is $-G^1-G^2-G^3-$;

G^1 is (1) C1-4 straight-chain alkylene optionally substituted by 1 to 2 C1-4 alkyl(s), (2) C2-4 straight-chain alkenylene optionally substituted by 1 to 2 C1-4 alkyl(s) or (3) C2-4 straight-chain alkynylene optionally substituted by 1 to 2 C1-4 alkyl(s);

G^2 is (1) -Y-, (2) -ring1-, (3) -Y-ring1-, (4) -ring1-Y- or (5) -Y-C1-4 alkylene-ring1-;

Y is (1) -S-, (2) -SO-, (3) $-SO_2-$, (4) -O- or (5) $-NR^1-$;

R^1 is (1) a hydrogen atom, (2) C1-10 alkyl or (3) C2-10 acyl;

G^3 is (1) a bond, (2) C1-4 straight-chain alkylene optionally substituted by 1 to 2 C1-4 alkyl(s), (3) C2-4 straight-chain alkenylene optionally substituted by 1 to 2 C1-4 alkyl(s) or (4) C2-4 straight-chain alkynylene optionally substituted by 1 to 2 C1-4 alkyl(s);

D is D^1 or D^2;

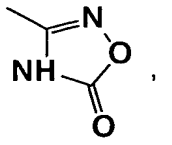
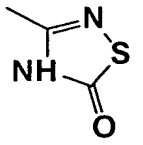
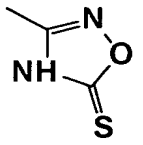
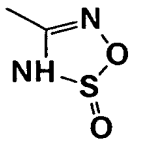
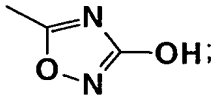
D^1 is (1) -COOH, (2) $-COOR^2$, (3) tetrazol-5-yl or (4) $-CONR^3SO_2R^4$;

R^2 is (1) C1-10 alkyl, (2) phenyl, (3) C1-10 alkyl substituted by phenyl or (4) biphenyl;

R^3 is (1) a hydrogen atom or (2) C1-10 alkyl;

R^4 is (1) C1-10 alkyl or (2) phenyl;

D^2 is (1) $-CH_2OH$, (2) $-CH_2OR^5$, (3) hydroxy, (4) $-OR^5$, (5) formyl, (6) $-CONR^6R^7$, (7) $-CONR^6SO_2R^8$, (8) -CO-(NH-amino acid residue-CO)$_m$-OH, (9) -O-(CO-amino acid residue-NH)$_m$-H, (10) $-COOR^9$, (11) $-OCO-R^{10}$, (12) $-COO-Z^1-Z^2-Z^3$, or

(13)  ,  ,  ,  , or  ;

R^5 is C1-10 alkyl;

R^6 and R^7 are, each independently, (1) a hydrogen atom or (2) C1-10 alkyl;

R^8 is C1-10 alkyl substituted by phenyl;

R^9 is (1) C1-10 alkyl substituted by biphenyl optionally substituted by 1 to 3 substituent(s) selected from C1-10 alkyl, C1-10 alkoxy and halogen or (2) biphenyl substituted by 1 to 3 substituent(s) selected from C1-10 alkyl, C1-10 alkoxy and halogen atom;

R^{10} is (1) phenyl or (2) C1-10 alkyl;

m is 1 or 2;

Z^1 is (1) C1-15 alkylene, (2) C2-15 alkenylene or (3) C2-15 alkynylene;

Z^2 is (1) -CO-, (2) -OCO-, (3) -COO-, (4) -$CONR^{Z1}$-, (5) -$NR^{Z2}CO$-, (6) -O-, (7) -S-, (8) -SO_2-, (9) -SO_2-NR^{Z2}-, (10) -$NR^{Z2}SO_2$-, (11) -NR^{Z3}-, (12) -$NR^{Z4}CONR^{Z5}$-, (13) -$NR^{Z6}COO$-, (14) -$OCONR^{Z7}$- or (15) -OCOO-;

Z^3 is (1) a hydrogen atom, (2) C1-15 alkyl, (3) C2-15 alkenyl, (4) C2-15 alkynyl, (5) ringZ or (6) C1-10 alkyl substituted by C1-10 alkoxy, C1-10 alkylthio, C1-10 alkyl-NR^{Z8}- or ringZ;

ringZ is (1) C3-15 mono-, bi- or tri-carbocyclic aryl which may be partially or fully saturated or (2) 3- to 15-membered mono-, bi- or tri-heterocyclic aryl which may be partially or fully saturated and contains 1 to 4 hetero atom(s) selected from oxygen, nitrogen and sulfur atom(s);

R^{Z1}, R^{Z2}, R^{Z3}, R^{Z4}, R^{Z5}, R^{Z6}, R^{Z7} and R^{Z8} are, each independently, a hydrogen atom or C1-15 alkyl;

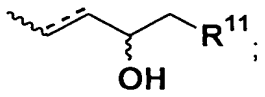
R^{Z1} and Z^3 may be taken together with the nitrogen atom to which they are attached to form a 5- to 7-membered saturated mono-heterocyclic ring, and the heterocyclic ring may contain other one hetero atom selected from oxygen, nitrogen and sulfur atoms;

ringZ and the saturated mono-heterocyclic ring formed by R^{Z1}, Z^3 and the nitrogen atom to which they are attached may be substituted by 1-3 groups selected from following (1) to (4):

(1) C1-15 alkyl, (2) C2-15 alkenyl, (3) C2-15 alkynyl, (4) C1-10 alkyl substituted by C1-10 alkoxy, C1-10 alkylthio or C1-10 alkyl-NR^{Z9}-;

R^{Z9} is a hydrogen atom or C1-10 alkyl;

E is E^1 or E^2;

E^1 is  ;

R^{11} is (1) C1-10 alkyl, (2) C1-10 alkylthio, (3) C1-10 alkyl substituted by C3-8 cycloalkyl, (4) C1-10 alkyl substituted by ring2 or (5) C1-10 alkyl substituted by -W^1-W^2-ring2;

W^1 is (1) -O-, (2) -S-, (3) -SO-, (4) -SO_2-, (5) -NR^{11-1}-, (6) carbonyl, (7) -$NR^{11-1}SO_2$-, (8) carbonylamino or (9) aminocarbonyl;

R^{11-1} is (1) a hydrogen atom, (2) C1-10 alkyl or (3) C2-10 acyl;

W^2 is (1) a bond or (2) C1-8 alkyl optionally substituted by C1-4 alkyl, halogen or hydroxy;

E^2 is (1) U^1-U^2-U^3 or (2) ring4;

U^1 is (1) C1-4 alkylene, (2) C2-4 alkenylene, (3) C2-4 alkynylene, (4) -ring3-, (5) C1-4 alkylene-ring3-, (6) C2-4 alkenylene-ring3- or (7) C2-4 alkynylene-ring3-;

U^2 is (1) a bond, (2) -CH_2-, (3) -CHOH-, (4) -O-, (5) -S-, (6) -SO-, (7) -SO_2-, (8) -NR^{12}-, (9) carbonyl, (10) -$NR^{12}SO_2$-, (11) carbonylamino or (12) aminocarbonyl;

R^{12} is (1) a hydrogen atom, (2) C1-10 alkyl or (3) C2-10 acyl;

U^3 is (1) C1-8 alkyl optionally substituted by 1 to 3 substituent(s) selected from C1-10 alkyl, halogen, hydroxy, alkoxy, alkylthio and $NR^{13}R^{14}$, (2) C2-8 alkenyl optionally substituted by 1 to 3 substituent(s) selected from C1-10 alkyl, halogen, hydroxyl, alkoxy, alkylthio and -$NR^{13}R^{14}$, (3) C2-8 alkynyl optionally substituted by 1 to 3 substituent(s) selected from C1-10 alkyl, halogen, hydroxy, alkoxy, alkylthio and -$NR^{13}R^{14}$, (4) C1-8 alkyl substituted by ring4 or (5) ring4;

R^{13} and R^{14} are, each independently, (1) a hydrogen atom or (2) C1-10 alkyl;

ring1, ring2, ring3 or ring4 may be substituted by 1 to 5 R;

R is (1) C1-10 alkyl, (2) C2-10 alkenyl, (3) C2-10 alkynyl, (4) C1-10 alkoxy, (5) C1-10 alkylthio, (6) halogen, (7) hydroxy, (8) nitro, (9) -$NR^{15}R^{16}$, (10) C1-10 alkyl substituted by C1-10 alkoxy, (11) C1-10 alkyl substituted by 1 to 3 halogen atom(s), (12) C1-10 alkyl substituted by C1-10 alkoxy substituted by 1 to 3 halogen atom(s), (13) C1-10 alkyl substituted by -$NR^{15}R^{16}$, (14) ring5, (15) -O-ring5, (16) C1-10 alkyl substituted by ring5, (17) C2-10 alkenyl substituted by ring5, (18) C2-10 alkynyl substituted by ring5, (19) C1-10 alkoxy substituted by ring5, (20) C1-10 alkyl substituted by -O-ring5, (21) $COOR^{17}$, (22) C1-10 alkoxy substituted by 1 to 4 halogen atom(s), (23) formyl, (24) C1-10 alkyl substituted by hydroxy or (25) C2-10 acyl;

R^{15}, R^{16} and R^{17} are, each independently, (1) a hydrogen atom or (2) C1-10 alkyl;

ring5 may be substituted by 1 to 3 substituent(s) selected from following (1)-(9):

(1) C1-10 alkyl, (2) C2-10 alkenyl, (3) C2-10 alkynyl, (4) C1-10 alkoxy, (5) C1-10 alkyl substituted by C1-10 alkoxy, (6) halogen atom, (7) hydroxy, (8) C1-10 alkyl substituted by 1 to 3 halogen atom(s), (9) C1-10 alkyl substituted by C1-10 alkoxy substituted by 1 to 3 halogen atom(s);

ring1, ring2, ring3, ring4 and ring5 are, each independently,

(1) C3-15 mono-, bi- or tri-carbocyclic aryl which may be partially or fully saturated or (2) 3- to 15-membered mono-, bi- or tri-heterocyclic aryl which may be partially or fully saturated and contains a hetero atom(s) selected from 1 to 4 nitrogen, 1 to 2 oxygen and/or 1 to 2 sulfur atom(s); and

wherein

1) when E is E^2, E^2 is U^1-U^2-U^3, and U^1 is C2 alkylene or C2 alkenylene, U^2 is not -CHOH-,

2) when U^3 is C1-8 alkyl substituted by at least one hydroxy, U^1-U^2 is not C2 alkylene or C2 alkenylene,

3) when A is A^1 and D is D^1, then E is not E^1,

4) when T is oxygen atom, X is $-CH_2-$, D is D^1, D^1 is COOH, A is A^1, A^1 is C2-8 straight-chain alkylene, E is E^2, E^2 is U^1-U^2-U^3, U^1 is C1-4 alkylene and U^3 is C1-8 alkyl, then U^2 is not a bond, $-CH_2-$, $-NR^{12}-$ or carbonyl,

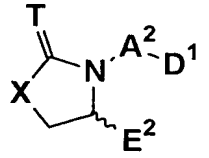
5) when T is an oxygen atom, X is $-CH_2-$, D is D^1, D^1 is COOH, A is A^2, G^1 is C1-4 alkylene, G^2 is -O- or $-NR^1-$, G^3 is a bond or C1-4 alkylene, E is E^2, E^2 is U^1-U^2-U^3, U^1 is C1-4 alkylene and U^3 is C1-8 alkyl, the U^2 is not a bond, $-CH_2-$, $-NR^{12}-$ or carbonyl,

6) when T is an oxygen atom, X is $-CH_2-$, D is D^1, E is E^2, E^2 is U^1-U^2-U^3, U^1 is C2 alkylene or C2 alkenylene and U^2 is -CO-, then A is not A^1,

7) 4-[(2-{(2R)-2-[(1E,3S)-3-hydroxy-oct-1-enyl]-5-oxo-pyrrolidin-1-yl}ethyl)thio]butanoic acid and 4-{2-[(R)-2-((E)-3-hydroxy-oct-1-enyl)-5-oxo-pyrrolidin-1-yl]-ethyl}-benzoic acid are excluded,

a pharmaceutically acceptable salt thereof or a cyclodextrin clathrate thereof.

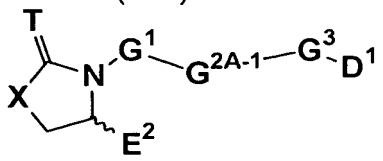
2. The 8-azaprostaglandin derivative compound according to claim 1, which is represented by formula (I-A):



(I-A)

wherein all symbols have the same meanings as described in claim 1, a pharmaceutically acceptable salt thereof or a cyclodextrin clathrate thereof.

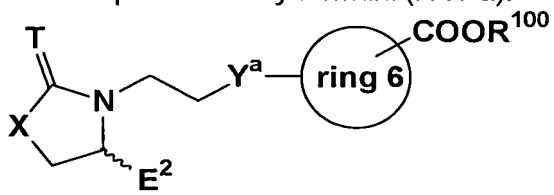
3. The 8-azaprostaglandin derivative compound according to claim 1 or 2, which is represented by formula (I-A1):



(I-A1)

wherein G^{2A-1} is $-Y^a$-ring1-, Y^a is -S-, $-SO_2$-, -O- or $-NR_1$-, and other symbols have the same meanings as described in claim 1, a pharmaceutically acceptable salt thereof or a cyclodextrin clathrate thereof.

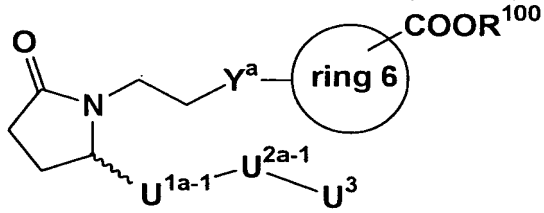
4. The 8-azaprostaglandin derivative compound according to any one of claims 1 to 3, which is represented by formula (I-A1-a):



(I-A1-a)

wherein ring6 is C5 or 6 mono-carbocyclic aryl, or 5- or 6-membered mono-heterocyclic aryl which may be partially or fully saturated and contains a hetero atom(s) selected from 1 to 4 nitrogen, 1 to 2 oxygen, and/or 1 to 2 sulfur atom(s); R^{100} is a hydrogen atom or C1-4 alkyl; and other symbols have the same meanings as described in claim 3, a pharmaceutically acceptable salt thereof or a cyclodextrin clathrate thereof.

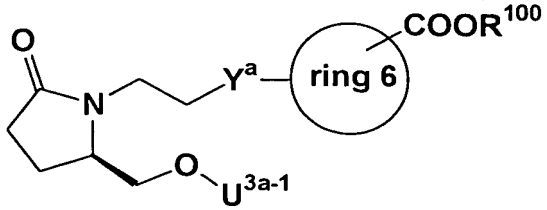
5. The 8-azaprostaglandin derivative compound according to any one of claims 1 to 4, which is represented by formula (I-A1-a1):



(I-A1-a1)

wherein U^{1a-1} is C1-4 alkyl, C2-4 alkenyl or C2-4 alkynyl, U^{2a-1} is -O-, -S-, -SO-, $-SO_2$- or $-NR^{12}$-, and other symbols have the same meanings as described in claim 4, the pharmaceutically acceptable salt thereof or the cyclodextrin clathrate thereof.

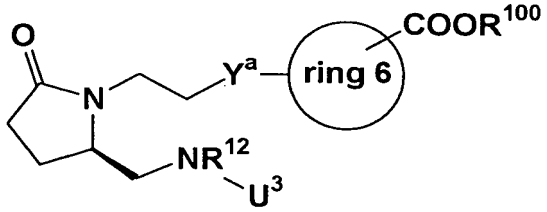
6. The 8-azaprostaglandin derivative compound according to any one of claims 1 to 5, which is represented by formula (I-a1-1):



(I-a1-1)

wherein U^{3a-1} is C1-8 alkyl or ring4, and other symbols have the same meanings as described in claim 4, a pharmaceutically acceptable salt thereof or a cyclodextrin clathrate thereof.

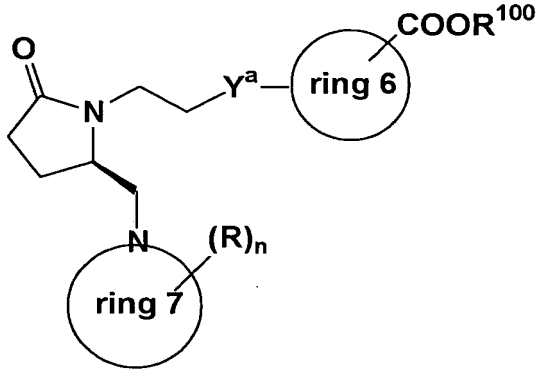
7. The 8-azaprostaglandin derivative compound according to any one of claims 1 to 5, which is a compound represented by formula (I-a1-2):



(I-a1-2)

wherein all symbols have the same meanings as described in claim 4, a pharmaceutically acceptable salt thereof or a cyclodextrin clathrate thereof.

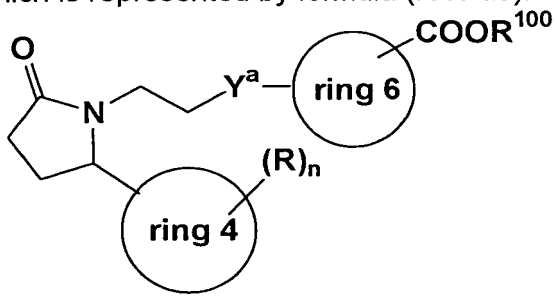
8. The 8-azaprostaglandin derivative compound according to any one of claims 1 to 4, which is represented by formula (I-A1-a2):



(I-A1-a2)

wherein ring7 is 3- to 15-membered mono-, bi- or tri-heterocyclic aryl which may be partially or fully saturated and contains at least one nitrogen atom and furthermore optionally 1 to 2 oxygen, and/or 1 to 2 sulfur atom(s); n is an integer from 1 to 3. Other symbols have the same meanings as described in claim 4, a pharmaceutically acceptable salt thereof or a cyclodextrin clathrate thereof.

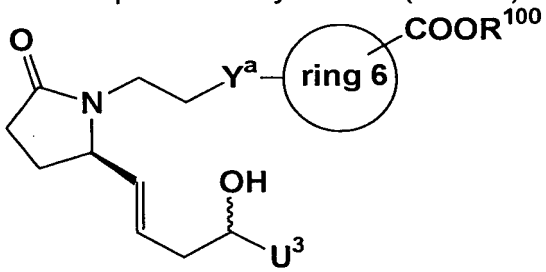
9. The 8-azaprostaglandin derivative compound according to any one of claims 1 to 4, which is represented by formula (I-A1-a3):



(I-A1-a3)

wherein all symbols have the same meanings as described in claim 8, a pharmaceutically acceptable salt thereof or a cyclodextrin clathrate thereof

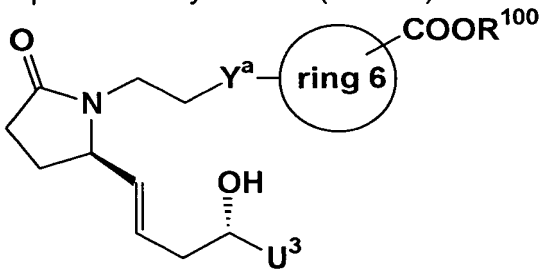
10. The 8-azaprostaglandin derivative compound according to any one of claims 1 to 4, which is represented by formula (I-A1-a4):



(I-A1-a4)

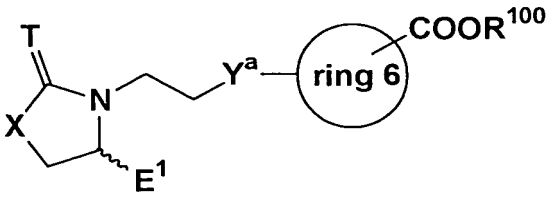
wherein all symbols have the same meanings as described in claim 4, a pharmaceutically acceptable salt thereof or a cyclodextrin clathrate thereof.

11. The 8-azaprostaglandin derivative compound according to claim 10, wherein the compound represented by formula (I-A1-a4) is:



wherein all symbols have the same meanings as described in claim 4, a pharmaceutically acceptable salt thereof or a cyclodextrin clathrate thereof.

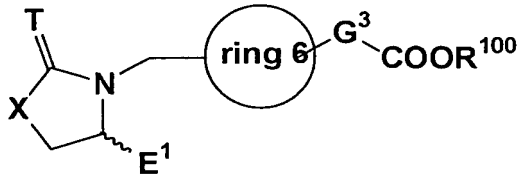
12. The 8-azaprostaglandin derivative compound according to claim 1, which is represented by formula (I-E1):



(I-E1)

wherein all symbols have the same meanings as described in claim 4, a pharmaceutically acceptable salt thereof or a cyclodextrin clathrate thereof.

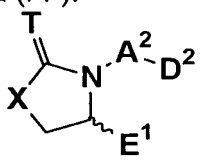
13. The 8-azaprostaglandin derivative compound according to claim 1, which is represented by formula (I-E2):



(I-E2)

wherein all symbols have the same meanings as described in claim 4, a pharmaceutically acceptable salt thereof or a cyclodextrin clathrate thereof.

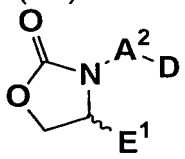
14. The 8-azaprostaglandin derivative compound according to claim 1, which is represented by formula (I-F):



(I-F)

wherein all symbols have the same meanings as described in claim 1, a pharmaceutically acceptable salt thereof or a cyclodextrin clathrate thereof.

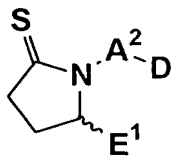
15. The 8-azaprostaglandin derivative compound according to claim 1, which is represented by formula (I-G):



(I-G)

wherein all symbols have the same meanings as described in claim 1, a pharmaceutically acceptable salt thereof or a cyclodextrin clathrate thereof.

16. The 8-azaprostaglandin derivative compound according to claim 1, which is represented by formula (I-H):



(I-H)

wherein all symbols have the same meanings as described in claim 1, a pharmaceutically acceptable salt thereof or a cyclodextrin clathrate thereof.

17. The 8-azaprostaglandin derivative compound according to claim 1, which is the compound described in any one of Example 1 to 22, a pharmaceutically acceptable salt thereof or a cyclodextrin clathrate thereof.

18. A pharmaceutical composition, which comprises, as an active ingredient, the 8-azaprostaglandin derivative compound according to any one of claims 1 to 17, a pharmaceutically acceptable salt thereof or a cyclodextrin clathrate thereof.

19. The pharmaceutical composition according to claim 18, which is EP_2 and/or EP_4 receptor agonist.

20. A preventive and/or treatment agent for immune diseases, allergic diseases, neuronal cell death, dysmenorrhea, premature birth, abortion, baldness, retinal neuropathy, erectile dysfunction, arthritis, pulmonary injury, pulmonary fibrosis, pulmonary emphysema, bronchitis, chronic obstructive pulmonary disease, hepatic injury, acute hepatitis, liver cirrhosis, shock, nephritis, renal failure, circulatory diseases, systemic inflammatory response syndrome, sepsis, hemophagocytosis syndrome, macrophage activation syndrome, still disease, Kawasaki Disease, burn, systemic granuloma, ulcerative colitis, Crohn disease, hypercytokinemia at dialysis, multiple organ failure, or bone diseases, which comprises, as an active ingredient, the 8-azaprostaglandin derivative compound according to any one of claims 1 to 17, a pharmaceutically acceptable salt thereof or a cyclodextrin clathrate thereof.